HOW THE PURKINJE SYSTEM DETERMINES THE VENTRICULAR ACTIVATION SEQUENCE

R. W. Joyner

Department of Pediatrics, The Children's Heart Center,
Emory University School of Medicine, Atlanta, GA, USA

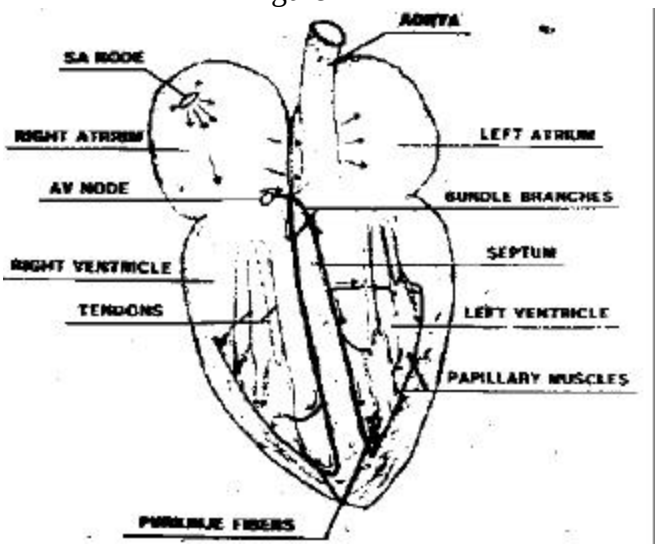
Abstract:

Conduction of the cardiac action potential in a spatially and temporally defined excitation sequence involves regional differences in cell membrane properties and intercellular coupling. This produces a sequence which in some regions is nearly continuous while other regions have discontinuous conduction. The Purkinje-Ventricular junction sites on the endocardial surface seem specifically designed to use discontinuous conduction as a means of effectively increasing the spread of activation through the endocardial surface while preserving a high safety factor for conduction. We present a historical survey of studies on this junctional region. Because of the specialized nature of the action potential properties of the Purkinje and ventricular as well as the localized electrical coupling, these sites may serve to originate arrhythmias as regions of after-depolarizations or may serve as important sites within endocardial reentrant circuits. In addition, the changes in the spatial pattern of junctional conductance following myocardial ischemia may produce other sites within the atrium or ventricle with properties of discontinuous conduction.

I. Introduction

The normal excitation sequence of the heart is dependent on the geometrical arrangement of different types of excitable cells as well as the spatial distribution and orientation of the gap junctions connecting these cells. Figure 1 illustrates the major pathway of normal excitation of the heart, with spontaneous activity in the sinoatrial node propagating through the walls of the atria, with conduction block occurring at the fibrous barrier between atrial and ventricular tissue except for the specialized tissue of the atrioventricular node. Following slow conduction through the node, excitation then enters specialized Purkinje system with excitation continuing down both sides of the ventricular septum and then up along the endocardial surface of both ventricles. From this endocardial Purkinje tissue, excitation spreads into the ventricular wall at specialized sites of interconnection between the Purkinje cells and the underlying ventricular muscle cells. Throughout this process, the excitation wave varies from a nearly continuous propagation with high velocity (in regions of high electrical coupling) to a clearly discontinuous process with significant delays over short distances (in regions of poor electrical coupling).

Figure 1



One normal region that has been characterized both with anatomical and electrophysiological studies as showing discontinuous conduction is the junctional region between the Purkinje (P) cells and the underlying endocardial ventricular muscle (VM) cells. While most of the P cells on the endocardial surface are electrically insulated from the underlying VM cells, the Purkinje-ventricular muscle Junctions (PVJs) are sites where sufficient electrical coupling allows action potential conduction from the P cells to the VM cells. The PVJ was first characterized as a "funnel" of increasing electrical load based on measuring 5 to 25 mSec delays in asymmetrical conduction from the P to the VM cells [1-5]. Subsequently, two-dimensional activation studies of the P and VM cell layers were made with surface electrodes and combined with microelectrode recordings[6-8] to more precisely locate junctional sites and to show that action potential conduction could be characterized as a "resistive barrier" in which transitional (T) cells coupled P cells to underlying VM cells. Results from histological studies [9,10], have confirmed these findings and the authors [10] described the PVJ of the Rabbit papillary muscle as a region in which an "intermediate sheet of transitional cells" couples the P cells to the VM cells as specific junctional sites.

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Abstract

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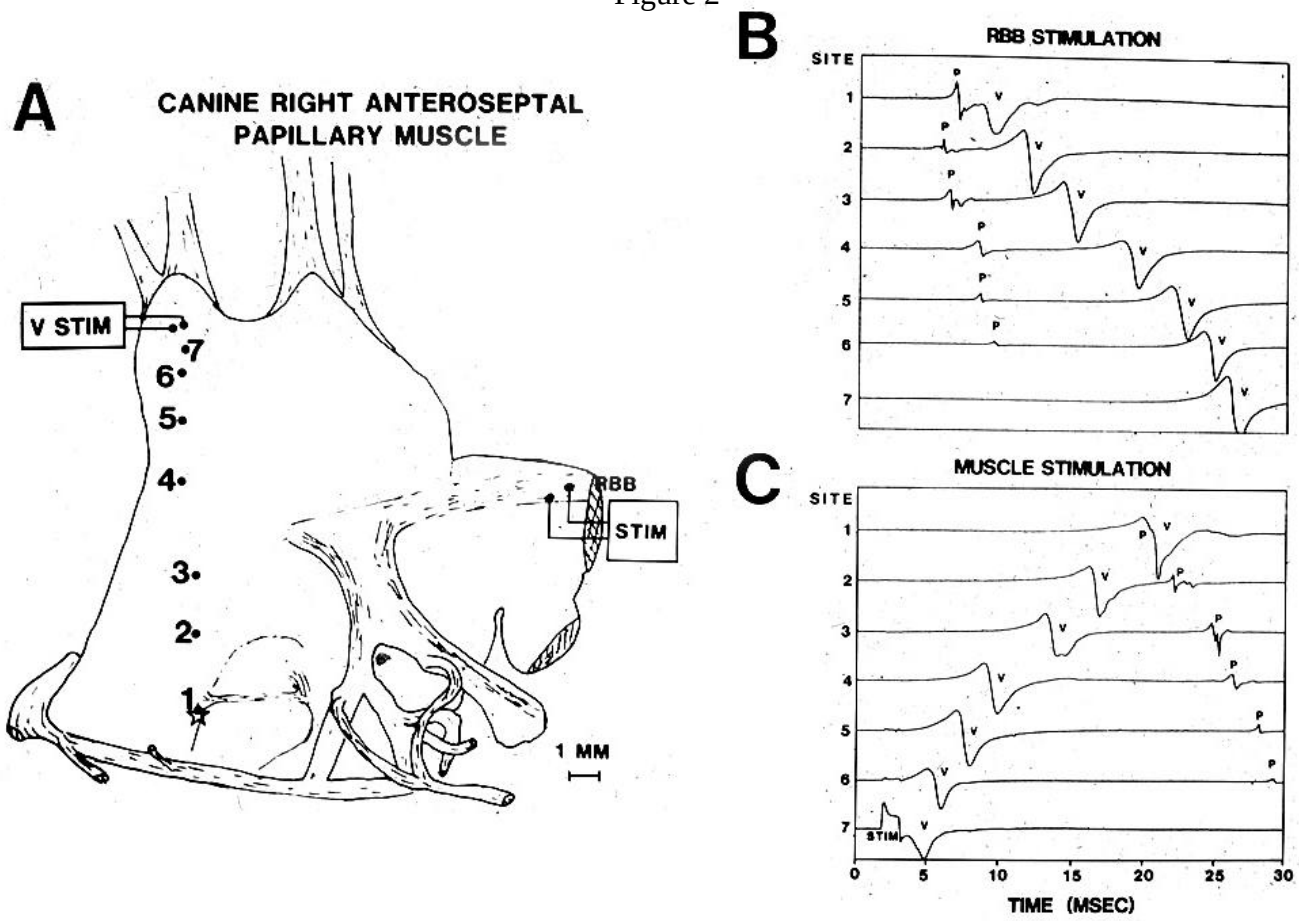
II. Results

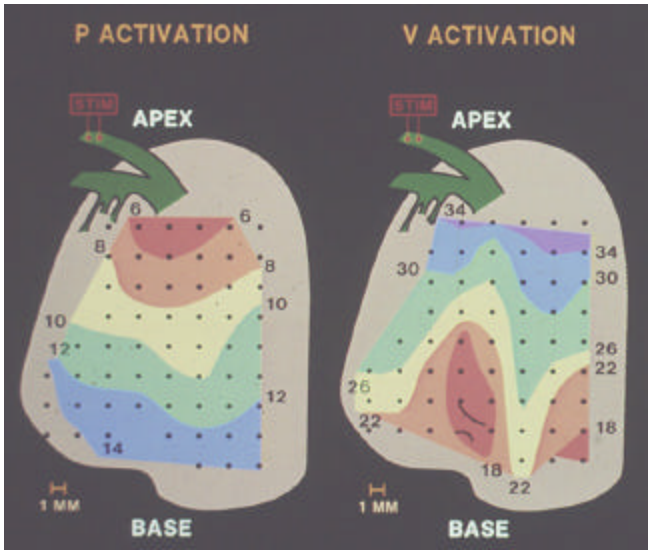
Figure 2 shows surface electrical recordings from an excised and superfused canine right anteroseptal papillary muscle. These electrical recordings were made with bipololar silver wires with each wire insulated with teflon except at the tip. For each bipolar electrode, one of the leads is touching the endocardial surface and the other lead is within the bath solution and about 0.5 mm above the surface of the muscle. The most superficial layer of cells throughout most of the ventricular endocardial surface are Purkinje cells but this layer is often only a few cells thick, so the endocardial electrodes record electrical activity both from these Purkinje cells and from the underlying ventricular muscle cells. For this experiment we placed seven of these bipolar electrodes in a line from the bottom to the top (labeled 1-7, see part A) of the papillary muscle and placed two stimulating electrodes: one stimulator on the right bundle branch (RBB) near its attachment to this papillary muscle and another stimulator near the top of the papillary muscle. For papillary muscles, the Purkinje layer generally does not extend all the way up to the tip of the muscle, so this second stimulator was directly stimulating the ventricular muscle cells. In Panel B, we show the results for stimulation on the RBB. Note that each of electrodes 1-6 has two distinct electrical signals that we showed (from other studies not shown) could be identified as the signal produced by the Purkinje layer (the 'P' signal) and the signal produced by the ventricular muscle layer (the 'V' signal). Propagation through the P layer moves from right to left across the muscle as shown, with nearly simultaneous arrival of activation at electrodes 1-6 for P activation. However, V activation follows a completely different time sequence, with initial activation of the V layer at electrode 1 and progression through electrodes 2,3,4,5,6, and 7. There are also characteristic differences in the waveform of the V signal. At the site of V activation from the P layer (electrode 1) the V signal is completely negative with a delay of 3-5 ms from the local P activation. At sites where the V layer has a propagating wave within the plane of the endocardial surface, the V signal is biphasic, with a positivity followed by a negativity. For the same papillary muscle and the same recording sites, a completely different pattern activity is observed when the stimulus is applied to the top of the muscle (near electrode site 7, as shown in Part C. Activity now occurs first at electrode 7 and then progresses through the V layer to electrode 1. As the V activation approaches electrode 1, the activation also propagates into the P layer and now a reversed sequence of

Figure 2



P activation occurs with activation from electrode 1 to electrode 6 in the P layer. From additional experiments (not shown) we showed that V to P conduction could always occur at PVJ sites but that there were some sites at which V to P conduction would occur even though these

Figure 3

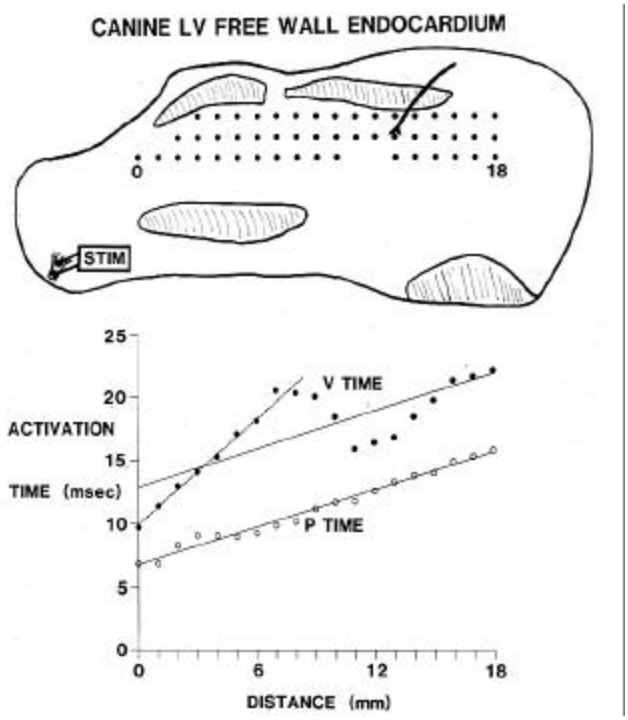


sites were not PVJ sites in the sense of directly allowing P to V conduction.

Figure 3 shows a two dimensional representation of this process from a canine left papillary muscle. From the left side of the septum, there are often free-running Purkinje strands which cross the ventricular cavity and connect with the sides or tips of the papillary muscle, as indicated in the diagram of the muscle. The left part shows the results of activation mapping by recordings from the sites shown as black dots for the time sequence of P layer activation, while the right part shows results of activation mapping for the time sequence of the ventricular layer for the same recording sites and stimulation location. Note that activation proceeds through the P layer until an anatomical site for P to V conduction is activated and only at that site does activation of the V layer occur. For papillary muscles, these sites are nearly always located at the base of the muscle, near its insertion into the endocardial wall. After ventricular activation occurs, propagation occurs through the V layer away from the PVJ site. Note also that the intrinsic conduction velocity in the P layer is several times greater than in the V layer, as shown by the time difference for the isochronal lines.

This process of propagation from the P layer to the V layer only at specific junctional sites is not restricted to the papillary muscles, but also occurs over the endocardial free wall of both ventricles. Figure 4 illustrates this process and also demonstrates the consequence of this process for effective ventricular velocity within the endocardial plane. For this preparation, we stimulated the P layer as shown in the lower left of the diagram and recorded both P and V activation sequences at the points indicated as black dots. From these three horizontal lines of recording locations, we then averaged the time of activation of the P layer and the V layer as functions of horizontal distance. For this preparation, there was a single PVJ site near the center of the preparation. The graph shows the averaged P activation times as open circles and the averaged V activation times as solid circles. Note that at each horizontal location the P activation precedes the V activation. The P activation times form a straight line, indicating a nearly constant P velocity (the inverse of the slope of the activation line). The sequence of V activation times forms a more complex relationship, with much slower velocity (greater slope of the activation line) away from the PVJ site and then a re-synchronization of the V activation at the PVJ site. Note that for activation times between 15 and 22 ms there are actually three simultaneous ventricular activation processes, one moving from left to right on the left side of the PVJ site, a second activation moving from right to left

Figure 4



to the left of the PVJ site and a third moving from left to right on the right side of the PVJ site. The net result is that the effective velocity of propagation through the V layer is increased to be nearly equal to that of the P layer, thus increasing the velocity within the V layer.

Another consequence of the discontinuous nature of the endocardial V layer conduction is that the sensitivity of this conduction to pharmacological agents is greater than that for the P layer or the V layer alone. There is an increased sensitivity of the junctional site (as compared to the regions of continuous conduction) to Quinidine [8], elevated potassium, hypoxia and low pH [11,12]. We also showed [12] that PVJ delay was significantly affected by

combinations of low pH, elevated potassium (from 4 to 8 mM), hypoxia, and/or rapid pacing (BCL from 1000 to 400 mSec) even when these agents were having minimal effects on continuous conduction (within the Purkinje or the Ventricular Muscle layers) of the same preparations. In particular the combination of low pH and elevated potassium (BCL 1000 mSec) lowered Purkinje velocity by 23% and increased PVJ delay by a similar 31%. The addition of hypoxia decreased Purkinje velocity by 26% from control while PVJ delay was increased 106% from control. The further addition of rapid pacing increased PVJ delay 199% from control while the Purkjinje velocity was decreased only 26% from control. However, the same degree of hypoxia applied at normal pH and potassium concentration had almost no effect on either Purkinje velocity or PVJ delay. These results are partly explained by the dependence of continuous conduction on the L-type calcium current [13] and the well known dependence of the calcium current on metabolic support and the slowed recovery from inactivation of the calcium current. We recently showed [14] that PVJ delay is decreased by Isoproterenol and this effect is blocked by Carbachol, consistent with other studies on discontinuous conduction.

III. Conclusions

Studies on PVJ conduction are of fundamental interest to the understanding of cardiac conduction abnormalities for several reasons: **First**, they represent studies on intact tissue which has been shown to produce discontinuous conduction under normal conditions. **Second**, the discontinuous conduction at the PVJ is asymmetrical, with shorter delays when conducting retrograde (from VM cells to P cells) than for antegrade conduction. **Third**, microelectrode recordings can be made from T cells which have been shown to be anatomically placed between the P and VM cells and which can be identified by the characteristic partial repolarization during conduction and their timing of activation with respect to the surface recordings. **Fourth**, the surface recordings not only produce a time sequence of local activation but also indicate the characteristics of local activation as occurring directly at the local site (from P cells through T cells to VM cells, producing an all-negative VM signal) or occurring within the VM layer as a propagating wave from a remote junctional site (producing a biphasic VM signal), and **fifth**., the interactions between the Purkinje layer and the underlying ventricular muscle cells may be of significance in the initiation of arrhythmias involving early or delayed after-depolarizations or endocardial reentry.

Reference List

[1] J. Alanis and D. Benitez. Transitional potentials and the propagation of impulses through different cardiac cells. In: *Electrophysiology and Ultrastructure of the Heart*, eds. T. Sano, V. Misuhira, and K. Matsuda. Tokyo,Japan: Bunkoko Co.,Ltd., 1967.

[2] C. Mendez, W.J. Mueller, J. Meredith, and G.K. Moe, Interaction of transmembrane potentials in canine purkinje fibers and at purkinje fiber-muscle junctions *Circ.Res.*, vol. 24, pp. 361-373, 1969.

[3] C. Mendez, W.J. Mueller, and X. Urguiaga, Propagation of impulses acreoss the purkinje fiber-muscle junctions in the dog heart *Circ.Res.*, vol. 26, pp. 135-150, 1970.

[4] R.J. Myerburg, J.S. Cameron, N.J. Lodge, S. Kimura, N. Saoudi, P.L. Kozlovskis, and A.L. Bassett. The papillary musle preparation in a study of cardiac electrophysiology, electropharmacology, and disease models. In: *Cardiac electrophysiology and arrhythmias*, eds. D.P. Zipes and J. Jalife. Orlando, FL: Grune & Stratton, 1985.pp. 225-231.

[5] R.J. Myerburg, K. Nilsson, and H. Gelband, Physiology of canine interventricular conduction and endocardial excitation *Circ.Res.*, vol. 30, pp. 217-243, 1972.

[6] E.D. Overholt, R.W. Joyner, R.D. Veenstra, D. Rawling, and R. Weidmann, Unidirectional block between purkinje and ventricular layers of papillary muscle *Am.J.Physiol.*, vol. 247, pp. H584-H5951984.

[7] D.A. Rawling and R.W. Joyner, Characteristics of the junctional regions between Purkinje and ventricular muscle cells of the canine ventricular subendocardium *Circ.Res.*, vol. 60, pp. 580-585, 1987.

[8] R.D. Veenstra, R.W. Joyner, and D.A. Rawling, Purkinje and ventricular activation sequences of canine papillary muscle. Effects of quinidine and calcium on the purkinje-ventricular conduction delay *Circ.Res.*, vol. 54, pp. 500-515, 1984.

[9] A. Martinez-Palomo, J. Alanis, and D. Benitez, Transitional cells of the conduction system of the dog heart *J.Cell.Biol.*, vol. 47, pp. 1-17, 1970.

[10] J. Tranum-Jensen, A.A. Wilde, J.T. Vermeulen, and M.J. Janse, Morphology of electrophysiologically identified junctions between Purkinje fibers and ventricular muscle in rabbit and pig hearts *Circ.Res.*, vol. 69, pp. 429-437, 1991.

[11] R.F. Gilmour, J.J. Evans, and D.P. Zipes, Purkinje-muscle coupling and endocardial response to hyperkalemia, hypoxia, and acidosis *Am.J.Physiol.*, vol. 247, pp. H303-H3111984.

[12] R.D. Veenstra, R.W. Joyner, R.T. Wiedmann, M.L. Young, and R.C. Tan, Effects of hypoxia, hyperkalemia, and metabolic acidosis on canine subendocardial action potential conduction *Circ.Res.*, vol. 60, pp. 93-101, 1987.

[13] H. Sugiura and R.W. Joyner, Action potential conduction between guinea pig ventricular cells can be modulated by calcium current *Am.J.Physiol.*, vol. 263, pp. H1591-604, 1992.

[14] R.T. Wiedmann, R.C. Tan, and R.W. Joyner, Discontinuous conduction at Purkinje-ventricular muscle junction *Am.J.Physiol.*, vol. 271, pp. H1507-16, 1996.